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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2004900719 for a patent by CONVE LTD as filed on 16 February 2004.



WITNESS my hand this
Twenty-fifth day of February 2005

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ORIGINAL
AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: "Sperm-Active Preparations and Uses Thereof"

The invention is described in the following statement:

Sperm-Active Preparations and Uses Thereof

Field of the Invention

The present invention relates to the use of copper compositions active against sperm and in particular compositions that are able to kill or otherwise retard sperm motility. The present invention also relates to copper silicate formulations and contraceptive compositions adapted for topical administration comprising copper silicate. The present invention also relates to contraceptive devices impregnated or otherwise treated to contain copper silicate.

Background Art

10 The two most commonly used vaginal contraceptives are the non-ionic detergents nonoxynol-9 and octoxynol-9. These agents rely on the ability of detergents to lyse the sperm. However, detergents commonly cause side effects such as irritation and inflammation of body tissue such as the vaginal and cervical epithelium. Irritation of these tissues can render a subject more prone to STD's
15 including viral infections.

There exists a need for improved contraceptives which are sperm-active but do not suffer from the side-effects of currently available products. The present invention seeks to overcome the above problems by providing safe and effective sperm-active compositions, including topical formulations that can be used to
20 control sperm.

Summary of the Invention

The present invention provides a method of controlling sperm, the method comprising the step of contacting the sperm with an effective amount of copper silicate .

The ability of copper silicate to control sperm renders it useful in applications where it is desirable to reduce or totally remove sperm motility or otherwise inactivate sperm. One particular application where this activity is useful is in the production of contraceptives. Thus, the present invention also provides for the
5 use of an effective amount of copper silicate as a contraceptive.

The copper silicate used in the methods of the present invention may be formulated to render them particularly suitable for administration to mammals such as humans. Thus, the present invention also provides for the use of copper silicate for the preparation of a formulation for use as a contraceptive and a
10 composition adapted for topical administration comprising an effective amount of copper silicate wherein the effective amount is sufficient to act as a contraceptive.

The copper silicate used in the method of the present invention may also be combined or otherwise integrated into existing contraceptive devices such as barrier agents to improve their effectiveness as a contraceptive. Thus, the
15 present invention also provides a contraceptive device comprising copper silicate.

Brief Description of the Figures

Figure 1 is a table setting out the results of an assay for spermicidal activity of four compositions according to the invention; and

Figure 2 is a table setting out the results of an assay for cervical mucous blocking
20 activity of four compositions according to the invention.

Detailed Description of the Invention

Methods of controlling sperm

The present invention provides a method of controlling sperm, the method comprising the step of contacting the sperm with an effective amount of copper
25 silicate.

For the purposes of the present invention, the phrase "controlling sperm" means one or more of the following: at least reducing sperm motility, at least reducing the number of viable sperm, at least reducing the ability to penetrate cervical mucous and killing sperm.

- 5 The ability of copper silicate to control sperm renders it useful as a contraceptive. The present invention also provides for the use of an effective amount of copper silicate as a contraceptive.

When used as a contraceptive the copper silicate may be applied in a variety of ways so that it contacts and controls the sperm. For example the copper silicate
10 may be applied to a site expected to receive or come into contact with sperm. Thus, the site may be a body part such as a reproductive organ or part thereof and in particular the site may be part of the reproductive tract, the penis, vagina or cervix. Alternatively, the site may be a physical object such as another contraceptive agent such as a condom or the like or a sex aid.

- 15 The effective amount of the copper silicate applied in the method of the present invention will vary depending, at least, on the application site and the conditions at that site. However, it will at least be sufficient to control sperm. Examples of the amount of copper silicate product applied according to the method of the present invention are (i) weight range: 1-10g = mass (as copper) applied 0.01g -
20 0.30g; (ii) weight range: 2-8g = mass (as copper) applied: 0.02g - 0.25g; and (iii) weight range: 4-6g = mass (as copper) applied: 0.04g - 0.20g.

The frequency with which, and the duration for which, the copper silicate is applied will be sufficient to control sperm and thus will also vary depending at least on the site of application and the concentration of the copper silicate. It is
25 expected the copper silicate will be applied on a needs basis by the end user to meet specific requirements.

Formulations

To render them particularly suitable for application to mammals such as humans the copper silicate used in the methods of the present invention may be specially formulated. Thus, the present invention also provides for the use of copper
5 silicate for the preparation of a formulation for controlling sperm or use as a contraceptive.

The formulations of the present invention may be produced by dissolving or combining the copper silicate in an aqueous or non-aqueous carrier. In general, any liquid, cream, or gel, or similar substance that does not appreciably react with
10 the copper silicate or any other active ingredient that may be introduced and which is non-irritating is suitable.

The formulations may be adapted for administration via a range of routes. However, preferably, the formulations are adapted for topical administration. Thus, the present invention also provides a method of producing a compound
15 adapted for topical administration comprising the step of dissolving or combining copper silicate in an aqueous or non-aqueous topical carrier.

The present invention also provides a formulation adapted for topical administration comprising an effective amount of copper silicate.

The form of the copper silicate in the formulation of the present invention may be
20 varied provided it retains its ability to control sperm. Preferably, the copper silicate is present in the formulation as a solution. Acidified solutions, including aqueous solutions, are particularly preferred because copper silicate is more soluble at acidic pH. Particularly preferred pHs are 3-6, 4-6 and 5-6. However, it will be appreciated that the pH of the formulation should be physiologically
25 acceptable. The copper silicate may also be in solid form provided it is properly prepared. In this regard, the copper silicate could be in the form of a micronized solid such as chrysocolla.

The composition adapted for topical administration may be in the form of any one of the following: solution, lotion, suspension, emulsion, cream, gel, ointment, liniment and salve. Particularly preferred forms are ointments, creams or gels.

5 Ointments generally are prepared using either (1) an oleaginous base, *i.e.*, one consisting of fixed oils or hydrocarbons, such as white petroleum or mineral oil, or (2) an absorbent base, *i.e.*, one consisting of an anhydrous substance or substances that can absorb water, for example anhydrous lanolin. Customarily, following formation of the base, whether oleaginous or absorbent, the active ingredient is added to an amount affording the desired concentration.

10 Creams are oil/water emulsions. They consist of an oil phase (internal phase), comprising typically fixed oils, hydrocarbons and the like, waxes, petroleum, mineral oil and the like and an aqueous phase (continuous phase), comprising water and any water-soluble substances, such as added salts. The two phases are stabilised by use of an emulsifying agent, for example, a surface active agent,
15 such as sodium lauryl sulfate; hydrophilic colloids, such as acacia colloidal clays, veegum and the like. For the purposes of the present invention, the compound may be added to the water phase prior to formation of the emulsion, in an amount to achieve the desired concentration.

Gels comprise a base selected from an oleaginous base, water, or an emulsion-suspension base. To the base is added a gelling agent that forms a matrix in the
20 base, increasing its viscosity. Examples of gelling agents are hydroxypropyl cellulose, acrylic acid polymers and the like. For the purposes of the present invention the compound may be added to the formulation at the desired concentration at a point preceding addition of the gelling agent.

25 Preferably, the formulations of the present invention have lubricant characteristics. Thus, the present invention also provides a formulation adapted for topical administration comprising an effective amount of copper silicate wherein the formulation is adapted to also act as a lubricant. The formulations of the present invention will often have lubricant characteristics inherently due to

other agents in the formulation. However, this aspect of the invention also covers lubricants that have copper silicate incorporated therein.

The formulations of the present invention may further comprise an auxiliary agent such as any one or more of: preservatives, stabilizers, emulsifiers, wetting agents, 5 fragrances, colouring agents, odour controllers and thickeners such as natural gums.

The concentration of the copper silicate in the formulation may be varied as required and with reference to the intended end use. However, preferably, the concentration of the copper silicate is such that its final concentration is 10 approximately 0.01% - 10% w/w (as Cu). More preferably, the concentration of the copper silicate is to a final concentration of approximately 0.05% - 0.5% w/w (as Cu) or 0.05% - 0.3% (as Cu).

The formulations of the present invention include those that are adapted for delivery via a solid dosage form such as a tablet or suppository. Thus, the 15 present invention also provides a solid dosage form such as a tablet or suppository or the like comprising copper silicate or a formulation thereof.

Solid dosage forms suitable for the purposes of the present invention are described generally in *Martin, Remington's Pharmaceutical Sciences*, 18th Ed. (1990 Mack Publishing Co. Easton PA 18042) which is herein incorporated by reference. 20 These include tablets, capsules and pellets.

Disintegrants may be included in the solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatine, orange peel, 25 acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

An antifrictional agent may be included in the formulation to prevent sticking during the formulation process. Lubricants may be used as a layer between the copper silicate and the die wall and these can include but are not limited to: stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid
5 paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights and Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the composition during formulation and to aid rearrangement during compression might be added. The
10 glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the copper silicate into the aqueous environment, a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium
15 chloride or benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the
20 formulation of the compositions either alone or as a mixture in different ratios.

Controlled release formulations may be desirable. The compositions could be incorporated into an inert matrix that permits release by either diffusion or leaching mechanisms such as gums. Slowly degenerating matrices may also be incorporated into the formulation. Another form of a controlled release is by a
25 method where the copper silicate is enclosed in a semipermeable membrane that allows water to enter and push the copper silicate out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

A mix of materials might be used to provide the optimum film coating. Film coating
30 may be carried out in a pan coater or in a fluidised bed or by compression coating.

The copper silicate can also be included in the formulation as multiparticulates such as granules or pellets of particle size about 1mm. Thus, the invention further provides for formulations comprising microparticles, created from hydrophilic polymers, which contain copper silicate. The microparticles containing the copper
5 silicate may be made by a variety of methods known to those in the art, for example, solvent evaporation, desolvation, complex coacervation, polymer/polymer incompatibility and interfacial polymerisation.

Devices

The copper silicate may also be incorporated into other contraceptive devices
10 such as barrier agents to improve their contraceptive capacity. Thus, the present invention also provides a contraceptive device comprising copper silicate.

The devices of the present invention may be varied provided they are adapted to receive or be treated in a fashion that enables them to incorporate copper silicate and later make the copper or copper silicate bioavailable. Preferably, the device
15 is a barrier agent such as an agent selected from the group consisting of: sponges, films, cervical caps, diaphragms and condoms.

When the copper silicate is incorporated into a device it may be incorporated into the matrix of the material from which the device is made. This may be relatively simple in the case of a sponge. However, when the device is a condom
20 incorporating the copper silicate into the rubber matrix may involve some trial and error to ensure the copper is bioavailable. Regardless, a person skilled in the art can produce the devices of the present invention through routine trial and experiment.

The present invention will now be described with reference to the following
25 examples. The description of the examples is in no way to limit the generality of the preceding description.

Example 1

Materials/methods

The following products according to the invention were used in the examples.

Identifier	Description/Form	Approx. Cu content (as Cu % w/w)
CSG5	Gel formulation	0.188
CSG4	Gel formulation	0.094
CSL1	Lotion	0.24
CSSOL1	Solution	0.28

5

All these products contain copper in the form of soluble copper silicate (CuSiO_3). The formulations all use a concentrated solution of copper silicate as the source of the active copper silicate.

CSC - Concentrated Copper Silicate Solution

Ingredient	% wt
Deionised Water	87.45
Copper sulfate pentahydrate	4.35
Acetic acid (90%)	3.60
Sodium silicate solution	4.60

10

CSSOL1

Ingredient	%wt
CSC	25.22
Water	74.73
Sodium alkyl ether sulfate	0.05

CSG4

15

Ingredient	%wt
Deionised Water	66.88
CSC	7.89
Triethanolamine	1.31
Carbopol Ultrez 10	3.55
Glycerine	10.45
Propylene Glycol	9.40
Germaben IIE	0.52

CSG5

Ingredient	%wt
Deionised Water	58.52
CSC	14.94
Triethanolamine	2.62
Carbopol Ultrez 10	3.55
Glycerine	10.45
Propylene Glycol	9.40
Germaben IIE	0.52

5 CSL1

Ingredient	%wt
Deionised Water	56.72
CSC	19.95
Triethanolamine	1.10
Carbopol Ultrez 10	1.89
Glycerine	9.97
Alcohol	6.98
Sodium hydroxide solution 18%	3.39

- The above formulations were used in a series of (i) Sander-Cramer assays (assessment of complete sperm immobilization during a 30-second, compound-sperm co-incubation); and (ii) cervical mucous (CM) penetration assays (compound is pre-incubated with a CM microcolumn for 30 minutes, after which sperm are introduced into the system; sperm migration through the mucous is compared to that of control).

Results

- The results are shown in the attached tables (see Figures 1 and 2 respectively).

The test formulations displayed an antispermatic effect, particularly in regard to sperm motility and the sperm's ability to penetrate cervical mucous, a key step in the *in vivo* fertilization process.

The present invention includes modifications and adaptations apparent to those skilled in the art. Furthermore, throughout the specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

DATED this SIXTEENTH day of FEBRUARY 2004.

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Applicant

10

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Figure 1

COMPOUND	SOLVENT	MODIFIED SANDER-CRAMER ASSAY				SOLUBILITY
		INITIAL CONC (% w/w as Cu)	HIGHEST SPERMICIDAL DILUTION (1/X)	M.E.C. (% w/w as Cu)	n	
CSG4	0.9% NaCl*	0.09	3.7±0.3	0.02	6	Blue-green gel
CSG5	0.9% NaCl*	0.16	2.7±0.4	0.06	6	Blue-green gel
CSSOL1	0.9% NaCl*	0.28	8.0±0.0	0.04	6	Blue solution
CSL1	0.9% NaCl*	0.22	8.0±0.0	0.03	6	Blue-green lotion

COMPOUND	SOLVENT	MODIFIED SANDER-CRAMER ASSAY				SOLUBILITY
		INITIAL CONC (mg/ml)	HIGHEST SPERMICIDAL DILUTION (1/X)	M.E.C. (mg/ml)	n	
Nonoxynol-9	0.9% NaCl*	1	8.0±0.0	0.125±0.000	6	OK - clear solution

M.E.C.=Minimum Effective Concentration

*Saline was pH to 5 with 0.1N HCl. This saline was used for serial dilutions also.

Figure 2

Compound	Concentration (dilution)	MOET	n
		% CTL	
CGS4	1:16	1.5±1.0	10
CGS5	1:16	13.9±6.0	10
CSL1	1:16	54.3±8.7	10
CSSOL1	1:16	17.7±3.6	10
0.9% NaCl		100.0±0.0	10

MOET: Modified One-End Test

%CTL: percent penetration of test sperm in cervical mucous as compared to that of solvent (0.9%NaCl) control spermatozoa.

Incubation volumes: 100ul Soln:100ul Adjusted Semen (60mill/mL)

Values represent Mean ± Standard Error.